PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Breast and cervical cancer patients' experience in Addis Ababa city, Ethiopia: A follow-up study protocol
AUTHORS	Gebremariam, Alem; Addissie, Adamu; Worku, Alemayehu; Hirpa, Selamawit; Assefa, Mathewos; Pace, Lydia; Kantelhardt, Eva; Jemal, Ahmedin

VERSION 1 - REVIEW

REVIEWER	Jennifer Moodley University of Cape Town, South Africa
REVIEW RETURNED	18-Oct-2018

GENERAL COMMENTS	Breast and cervical cancer patients' experience in Addis Ababa city, Ethiopia: A follow-up study protocol Reviewer report This article describes the protocol that will be used to follow up newly diagnosed breast and cervical cancer patients documenting patient experiences; patient, provider, diagnostic and treatment intervals; palliative care; survival and financial impact. The article is likely to be of interest to researchers in the field. The article could be improved by including some additional information in the protocol Abstract Page 2 Line 36 Could the authors clearly state the different outcomes of interest Page 2 Lines 38/39. The authors mention that qualitative data will be analyzed but this is the first time that qualitative research is being mentioned in the abstract. Strengths and Limitations Page 3 Line 27. This study will not capture all incident cases but rather approximately 90% as stated in the article. Introduction Page5 Line 30. Please indicate if TASH is a public or private sector hospital. Aims Page 6, Line 15/16. Are the investigators going to assess factors associated with these intervals?

	Study setting Please indicate the anticipated start date for the study. Can the authors add information on the proportion of the population that access public and private health care. Page 7 Line 5 – Indicate if the 8 study hospitals are in the public or private sector Study design and sample size. There is insufficient information on sample size calculations for the quantitative survey. to comment on whether the study is sufficiently powered to analyse the associations What is the anticipate refusal rate and anticipated loss to follow-up rate? It is not possible. Data collection tools and techniques Could the authors attach the English version of the quantitative questionnaire (draft or final) as a supplementary file. Page 8 line 3 – please state what patient related outcomes are being measured Line 9 – Is this a second tool or the second part of the questionnaire? Lines 11 – 18 Please indicate how the questions were adapted from these tools. Were the adapted tools validated for local use? Line 35 – Have the authors assessed how complete the medical records are in terms of the relevant variables being sought? Page 8 last paragraph. Can the authors expand on the qualitative data collection – are the investigators using any particular framework to guide their enquiry e.g. The Models of Pathways to Treatment proposed by Scott and Walters (British Journal of Health Psychology (2013), 18, 45–64.) Where will the qualitative interviews take place? How long will they last? Terms and Definitions Paragraph 3 Have the authors considered using calendar prompts? Data management and analysis plan Please clearly state what the independent variables are for the regression models Line 43 Please clearly state what specific time to event outcomes will be assessed. Page 12 Line 20 – 22. This last sentence is confusing. Ethics Please add information on how participant confidentiality will be maintained. Why are patients not giving written informed consent?

REVIEWER	Amos Deogratius Mwaka College of Health Sciences, Makerere University, Uganda
REVIEW RETURNED	31-Dec-2018

GENERAL COMMENTS	Dear Authors, I have read your study protocol with keenness. This is an important study that can potentially inform interventions to shorten

	time to help seeking and diagnosis of cancers and hence lead to timelier diagnosis and treatment of breast and cervical cancer thus improved survival. I do have a few concerns for you to clarify on: 1. In both the abstract and main document, you state that you will obtain verbal informed consents. It is important for you to justify the preference for verbal rather than written informed consent especially for the quantitative component of the study. I would be glad to read the ethics approval letter to better understand why verbal rather than written informed consents was approved. There is a prospective quantitative component to this study that perhaps requires you to interface with patients more than once. You will also require access to the treatment notes of the patients to extract key information including dates to enable calculations of time intervals, cancer stage at diagnosis and treatments received. I do suppose that these are confidential documents that need written consents from the patients to allow access for research purposes. 2. Under strength and limitations of the study, you do very well articulate the strengths but nowhere do I see you present any limitations. It is rare that a study does have no limitations. In your circumstance, obtaining actual dates when symptoms were first realized is a big limitation as it is for all studies on help seeking that rely on patient's recall of dates of events. If you do acknowledge this as a limitation, then you might want to explain how you will attempt to circumvent this, for example by using the calendar landmark approach. In addition, a great majority of patients' treatment nites have missing data when used in context of research because the original data were not collected to answer the specific research questions. You are doing a prospective study, could you design your data collection tool to capture all you need? 3. You do state that you will make phone calls to patients who may not be reachable for face-to-face interviews. You might as well want to explain a little more the ethical implications of making phone calls to cancer patients not reachable otherwise. For example, what will you do when you call the phone and you are received by a relative who is actively in grief because of the death of the same cancer patient? The phone call may come in when the relative has to a large extent overcome the pain of loss of a dear one to cancer and was moving on with life, but only for you to take the relative back the memory lane of pain and grief! Kindly reflect on this and provide readers with an explanation of how you will deal with such situation because you might meet it. 4. The analysis plan could be improved by setting out the plan objective by objective following the aims of the study as on page 6. For example, "For objective 1, we shall ..." 5. The study design could be explained a little better – prospective follow up study sounds rather vague to me. This has bearing on sample size calculations especially if the 450 and 250 are not necessary smaller than what a formula based sample size would provide. In otherwise, if there were so many cancer patients, what would you choose as your appropriate sample size? How do you arrive at that? It might be good to include this in the protocol even though for pragmatic reasons, you will recruit all available patients. Regards Amos

VERSION 1 – AUTHOR RESPONSE

Point by point response to reviewer(s)' comments:

Reviewer: #1 (Jennifer Moodley)

Comment #1: Page 2 Line 36 Could the authors clearly state the different outcomes of interest

Response: We now clarify the main outcomes of interest in the methods and analysis sub-section of the abstract (Page 2, line 7-8)

Comment #2: Page 2 Lines 38/39. The authors mention that qualitative data will be analyzed but this is the first time that qualitative research is being mentioned in the abstract.

Response: We now mention analysis of qualitative data in the first line of the Methods and analysis sub-section of the ABSTRACT (page 2)

Strengths and Limitations

Comment #3: Page 3 Line 27. This study will not capture all incident cases but rather approximately 90% as stated in the article.

Response: We thank the reviewer for this comment, and we have made the correction (page 3, bullet number 2)

Introduction

Comment #4: Page 5 Line 30. Please indicate if TASH is a public or private sector hospital.

Response: In the INTRODUCTION section, we have indicated TASH as “a referral public hospital” (page 5, 2nd paragraph)

Aims:

Comment #5: Page 6, Line 15/16. Are the investigators going to assess factors associated with these intervals?

Response: Yes, it is one of the specific objectives of the project. It is stated under the aims of the study bullet number 2 as “To assess factors associated with patient, diagnostic and treatment initiation time intervals for breast and cervical cancer patients” (Page 6)

Study setting

Comment #6:

Please indicate the anticipated start date for the study.

Response: We now have added a statement about start date of the study in the last sentence of study setting, which reads “Recruitment of the study participants has been started March 20, 2017” (Page 7, 2nd paragraph, last sentence)

Comment #7: Can the authors add information on the proportion of the population that access public and private health care.

Response: We now add this information in the study setting sub-section of the methods: According to a national survey, the main health care providers for outpatients was government health facilities (77%), followed by private health facilities (20%), traditional and religious healers (2%), and Non-governmental organization (1%). (page 7, 1st paragraph)

Comment #8: Page 7 Line 5 – Indicate if the 7 study hospitals are in the public or private sector

Response: We now add this information in the study setting sub-section of the methods (page 7, 2nd paragraph)

Study design and sample size

Comment #9: There is insufficient information on sample size calculations for the quantitative survey. to comment on whether the study is sufficiently powered to analyses the associations

Response: The estimation of sample size is described in the study design and sample size sub-section of the methods (page 8, 2nd paragraph).

Comment #10: What is the anticipate refusal rate and anticipated loss to follow-up rate? It is not possible.

Response: There may be patients who may not consent to participate in the study. But prior to the actual interview, we are providing them all the necessary information and let then choose convenient time for interview. As a result, so far, the rate of refusals is very small. To minimize the rate of lost to follow-up, we are capturing more than one contact addresses including the contact address of their relatives. We will use all possible options to trace the study participants.

Data collection tools and techniques

Comment #11: Could the authors attach the English version of the quantitative questionnaire (draft or final) as a supplementary file.

Response: The English version of the tool is attached as a supplementary file (Supplemental file 1: questionnaire)

Comment #12: Page 8 line 3 – please state what patient related outcomes are being measured

Response: We now list the types of patient related outcomes in the ‘Data collection tools and techniques’ sub-heading of the methods section as “this first phase of questionnaire also includes questions about patient reported outcomes (levels of fatigue, pain, sleep disorder, and depression) (page 8-9, 2nd paragraph)

Comment #13: Line 9 – Is this a second tool or the second part of the questionnaire?

Response: It is the second tool which will be administered at about one year after the diagnosis of the cases. We now clarify the statement in page 9, 2nd paragraph.

Comment #14: Lines 11 – 18 Please indicate how the questions were adapted from these tools. Were the adapted tools validated for local use?

Response: We have not empirically validated the tool for local use. The adapted questionnaire, however, was reviewed by local and international experts on the research subject and cancer care. Further, a pretest was performed to enhance the clarity of the tool (page 9, paragraph 1)

Comment #15: Line 35 – Have the authors assessed how complete the medical records are in terms of the relevant variables being sought?

Response: Yes, we have assessed the medical records of the patients whether the main variables considered in the study are captured. Since the project has a good data management system, most of the information are complete. Moreover, one of the co-author (MA) of this paper, is an oncologist in TASH, assessed our data extraction format in terms of availability of the variables of interest in the medical charts.

Comment #16: Page 8 last paragraph. Can the authors expand on the qualitative data collection?

Response: We have expanded on the qualitative data collection methods on page 9, last paragraph.

Comment #16: Where will the qualitative interviews take place? How long will they last?

Response: The qualitative interview will take place in one of the nursing offices at the oncology clinic, TASH. On average, we expect the interviews will last 30-40 minutes.

Terms and Definitions

Comment #17: Paragraph 3 Have the authors considered using calendar prompts?

Response: Yes, calendar prompts will be considered. We have indicated it under the 'term definitions and measurement' section, 3rd paragraph (page 11)

Data management and analysis plan

Comment #18: Please clearly state what the independent variables are for the regression models

Response: The independent variables are described under the 'term definitions and measurements' section, 1st paragraph (page 10)

Comment #19: Line 43 Please clearly state what specific time to event outcomes will be assessed.

Response: It is indicated in the description of method of analysis for specific objective 9 (page 15-16)

Comment #20: Page 12 Line 20 – 22. This last sentence is confusing.

Response: Apologies, it was a typo and we have corrected it (Page 13, last sentence of 'Qualitative data analysis'

Ethics

Comment #21: Please add information on how participant confidentiality will be maintained.

Response: We have now expanded this section by adding a statement "Only the principal investigators will have access to the deidentified data that will be kept in a secure place. All data will be coded without personal identifiers. All analyses will be on deidentified and coded data." (Page 17, 2nd paragraph).

Comment #22: Why are patients not giving written informed consent?

Response: Prior to the start of study subjects' recruitment, we conducted a rapid ethical assessment to design our consent process (ref. #55). Based on this assessment, we found that most of the participants were not comfortable to written consent for different reasons. Accordingly, we decided to use verbal consent, which has been approved by the IRB of College of Health Science of Addis Ababa University. (Page 17, 1st paragraph)

Reviewer #2 (Amos Deogratius Mwaka)

Comment #1. In both the abstract and main document, you state that you will obtain verbal informed consents. It is important for you to justify the preference for verbal rather than written informed consent especially for the quantitative component of the study. I would be glad to read the ethics approval letter to better understand why verbal rather than written informed consents was approved. There is a prospective quantitative component to this study that perhaps requires you to interface with

patients more than once. You will also require access to the treatment notes of the patients to extract key information including dates to enable calculations of time intervals, cancer stage at diagnosis and treatments received. I do suppose that these are confidential documents that need written consents from the patients to allow access for research purposes.

Response: Prior to the start of study subjects' recruitment, we conducted rapid ethical assessment to design our consent process (ref. # 55). Based on this assessment, we found that most of the participants were not comfortable to written consent for different reasons. Accordingly, we decided to use verbal consent, which has been approved by the IRB of College of Health Science of Addis Ababa University. (Page 17, 1st paragraph)

Comment #2. Under strength and limitations of the study, you do very well articulate the strengths but nowhere do I see you present any limitations. It is rare that a study does have no limitations. In your circumstance, obtaining actual dates when symptoms were first realized is a big limitation as it is for all studies on help seeking that rely on patient's recall of dates of events. If you do acknowledge this as a limitation, then you might want to explain how you will attempt to circumvent this, for example by using the calendar landmark approach. In addition, a great majority of patients' treatment nites have missing data when used in context of research because the original data were not collected to answer the specific research questions. You are doing a prospective study, could you design your data collection tool to capture all you need?

Response: We mention the limitation of the study on page 4, bullet number 6 and 7. Yes, we have tried to make our tool comprehensive enough to capture all the variables needed to address our specific objectives.

Comment #3. You do state that you will make phone calls to patients who may not be reachable for face-to-face interviews. You might as well want to explain a little more the ethical implications of making phone calls to cancer patients not reachable otherwise. For example, what will you do when you call the phone and you are received by a relative who is actively in grief because of the death of the same cancer patient? The phone call may come in when the relative has to a large extent overcome the pain of loss of a dear one to cancer and was moving on with life, but only for you to take the relative back the memory lane of pain and grief! Kindly reflect on this and provide readers with an explanation of how you will deal with such situation because you might meet it.

Response: We thank the reviewer for his comment. On page 17, we now reflect on the event of contacting when family members are grieving. The new addition reads" In the event family members are grieving when contacted for vital status, we will offer our condolences and ask then them if they will be willing to speak with us at a later time."

Comment #4. The analysis plan could be improved by setting out the plan objective by objective following the aims of the study as on page 6. For example, "For objective 1, we shall ..."

Response: We now have revised the planned objectives of the study as suggested by the reviewer (page 13-16)

Comment #5. The study design could be explained a little better – prospective follow up study sounds rather vague to me. This has bearing on sample size calculations especially if the 450 and 250 are not necessarily smaller than what a formula-based sample size would provide. In otherwise, if there were so many cancer patients, what would you choose as your appropriate sample size? How do you arrive at that? It might be good to include this in the protocol even though for pragmatic reasons, you will recruit all available patients.

Response: When we say prospective follow up study, we mean a cohort of cases will be recruited and followed prospectively for the development of the outcomes of interest over the study period. In our case, we will recruit and document the baseline characteristics of a cohort of newly diagnosis breast

and cervical cancer patients, and then after two years follow-up, we will assess the outcomes of interest, including survival. The reason we decided to enroll 450 breast and 250 cervical cancer cases is, based on previous reports, an estimated 450 breast and 250 cervical cancer incident cases were recorded each year in the city over the past two years. Thus, we decided to enroll these much cases to our study. However, we have also checked the adequacy of the estimated sample size (450 breast and 250 cervical cancer cases) to address the specific objectives of the project. We have included the description of the estimates of sample size required to address the specific objectives of the study under the 'study designs and sample size' sub heading, 2nd paragraph. (page 8).

VERSION 2 – REVIEW

REVIEWER	Jennifer Moodley University of Cape Town South Africa
REVIEW RETURNED	01-Feb-2019

GENERAL COMMENTS	Thank you, the authors have adequately addressed my comments.